**Table 1: Docking score and the interactions of the natural compounds with PLpro**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **S/N** | **Ligands** | **Binding Affinity ΔG (Kcal/mol)** | **Inhibition Constant Ki (µM) 10-6** | **Interacting Amino acids** | **Bond Type** |
|  | 3-deacetylsalanin | -6.0 | 46.4 | GLY 256, THR 259, THR 257, PHE 258, LYS 306, TYR 305, TYR 213, LYS 217, TYR 310, SER 309, GLU 307, ASN 308 | Van der waals, conventional hydrogen bond, Carbon hydrogen bond, Amide-Pi-Stacked, Pi-alkyl |
|  | Alpha terpineol | -4.9 | 289 | ASN 267, TYR 268, TYR 273, GLY 163, ASP 164, TYR 264, PRO 248, PRO 247, MET 208, THR 301 | Van der waals, Alkyl, Pi-Alkyl, Conventional Hydrogen Bond |
|  | Apigenin | -7.0 | 8.8 | TYR 251, LYS 254, THR 257, LYS 306, LYS 217, TYR 305, GLU 214, GLN 215, TYR 213, SER 212 | Van der waals, conventional hydrogen bond, Pi-Pi Stacked, Pi-Anion |
|  | Azadirachtin | -6.1 | 39.3 | GLU 167, LYS 157, GLN 269, LEU 162, TYR 273, TYR 264, TYR 268, GLY 163, MET 208, THR 301, PRO 247, PRO 248, ASP 164, ARG 166, GLU 161 | Van der waals, conventional hydrogen bond, Carbon Hydrogen Bond |
|  | Azadironic acid | -6.8 | 12.3 | GLN 250, LYS 297, TYR 251, SER 212, TYR 305, TYR 213, GLU 214, GLN 215, THR 257, LYS 254, GLU 252 | Van der waals, conventional hydrogen bond, Pi-Alkyl |
|  | Bornyl acetate | -5.0 | 245 | ASN 15, TYR 71, ILE 14, PRO 130, ASP 12, GLU 70, GLU 67 | Van der waals, conventional hydrogen bond, Alkyl, Pi-Alkyl |
|  | Buoebenone | -5.7 | 76.5 | PRO 247, MET 208, PRO 248, TYR 264, THR 301, TYR 273, ASP 164, TYR 268 | Van der waals, Pi-SigmaAlkyl, Pi-Alkyl |
|  | Carvone | -5.0 | 245 | ILE 314, PRO 316, GLU 318, THR 231, VAL 188, LYS 218, TYR 233, GLY 219 | Van der waals, Alkyl, Pi-Alkyl |
|  | Citral | -4.4 | 664 | TYR 233, THR 231, ILE 314, GLY 219, LYS 218, VAL 188, PRO 316, GLU 318, LEU 317 | Van der waals, Alkyl, Pi-Alkyl |
|  | Citronellol | -4.5 | 562 | LEU 80, SER 78, PRO 59, PHE 79, ASP 76, THR 74, ALA 68, THR 75, PHE 69, ARG 65, PRO 77 | Van der waals, conventional hydrogen bond, Alkyl, Pi-Alkyl |
|  | Copaene | -5.7 | 76.5 | LEU 317, GLU 318, PRO 316, TYR 233, VAL 188, THR 231, GLY 219, LYS 218, ILE 314 | Van der waals, Alkyl, Pi-Alkyl |
|  | Cryptone | -4.4 | 664 | LEU 64, ASP 61, GLN 19, THR 9, VAL 57, PHE 31, LEU 58, ASN 60 | Van der waals, conventional hydrogen bond, Alkyl |
|  | Cubebene | -5.4 | 126 | GLY 219, VAL 188, GLU 318, ILE 314, LEU 317, LYS 315, PRO 316, THR 231, TYR 233, LYS 218 | Van der waals, Alkyl, Pi-Alkyl |
|  | Cuminal | -4.8 | 342 | PRO 130, ILE 14, TYR 71, GLU 67, ASN 15 | Van der waals, conventional hydrogen bond, Carbon hydrogen bond Pi-Alkyl, Pi-Pi T-shaped, Alkyl |
|  | Cycloallin | -4.8 | 342 | PRO 248, THR 301, PRO 247, ASP 164, TYR 273, GLY 163, TYR 264, TYR 268 | Van der waals, conventional hydrogen bond, Carbon hydrogen bond |
|  | Decadienal | -3.8 | 1802 | PRO 316, VAL 188, LYS 190, ALA 230, THR 231, TYR 233, ILE 314, LYS 218 | Van der waals, conventional hydrogen bond, Alky |
|  | Gamma-s-propyl-cysteine | -3.7 | 2128 | SER 212, THR 257, PHE 258, LEU 253, TYR 305, VAL 303, TYR 251, TYR 213, GLU 214, GLN 215, LYS 218 | Van der waals, conventional hydrogen bond, Unfavorable Donor-Donor |
|  | Isohamnetin 3,4-diglucoside | -7.5 | 3.8 | ASP 179, ASN 128, PHE 173, LEU 178, ALA 176, ASN 177, HIS 73, THR 75, THR 74, TYR 154, HIS 175, GLN 174, GLU 203, LYS 200, VAL 202, GLY 201 | Van der waals, Conventional hydrogen bond, carbon hydrogen bond, Pi-Alkyl, Unfavorable Donor-Donor |
|  | Isorhamnetin 4-glucoside | -8.1 | 1.41 | GLU 307, TYR 310, LYS 306, PHE 258, TYR 305, THR 257, LYS 254, LEU 253, TYR 251, GLU 252, GLU 215, TYR 213, LYS 217 | Van der waals, Conventional hydrogen bond, Pi-Anion, |
|  | Isorhamnetin | -6.4 | 23.9 | PRO 247, ASP 164, TYR 268, GLN 269, LEU 162, LYS 157, GLY 163, TYR 273, PRO 248, THR 301, PRO 247 | Van der waals, conventional hydrogen bond, Pi-Anion |
|  | Isovallinin | -4.7 | 403 | GLU 214, TYR 213 | Conventional hydrogen bond |
|  | Kaempferol-3-O-rutinside | -7.3 | 5.4 | LEU178, LYS 200, GLY 201, GLU 203, ASN 128, GLN 174, HIS 73, HIS 175, PHE 69, TYR 154, ASN 156, PHE 79, ALA 153, ARG 82, ASP 76, PHE 173, VAL 202 | Van der waals, conventional hydrogen bond, Carbon Hydrogen Bond, Unfavorable donor-donor, Pi-Alkyl |
|  | Luteolin | -7.0 | 8.8 | GLY 163, TYR 264, PRO 247, ASN 267, GLY 266, PRO 248, TYR 268, THR 301, TYR 273, VAL 165, ASP 164, GLY 163 | Van der waals, conventional hydrogen bond, Pi-Pi Stacked, Pi-Alkyl |
|  | Meliacinin | -6.7 | 14.5 | GLN 174, TYR 171, ARG 166, MET 208, TYR 207, MET 206, SER 170, VAL 202, GLU 203 | Van der waals, conventional hydrogen bond, Alkyl |
|  | Methin | -4.4 | 664 | PHE 258, TYR 305, VAL 303, SER 212, TYR 213, GLU 214, GLU 252, LEU 253, LYS 254, THR 257, TYR 251 | Van der waals, conventional hydrogen bonds, Unfavorable donor-donor |
|  | Methychavicol | -4.6 | 476 | GLY 219, TYR 233, ILE 314, THR 231, LYS 190, GLU 318, VAL 188, PRO 316, LYS 218 | Van der waals, Pi-Alkyl, Alkyl, Pi-Sigma |
|  | Myrtenal | -5.1 | 207 | ASP 164, PRO 248, TYR 268, TYR 273, THR 301, ARG 166, ALA 246, MET 208, PRO 247, TYR 264 | Van der waals, conventional hydrogen bond, Alkyl, Pi-Alkyl |
|  | Nimbanal | -7.1 | 7.45 | MET 208, PRO 248, PRO 247, THR 301, ALA 246, TYR 273, TYR 264, GLY 163, ASP 164, TYR 268, GLN 269, LEU 162, GLU 167, ARG 166 | Van der waals, Carbon hydrogen bond, Pi-Sigma, Alkyl |
|  | Nimbionol | -6.6 | 17.1 | LYS 297, GLU 252, TYR 251, LYS 254, LEU 253, TYR 305, PHE 258, THR 257, VAL 303, TYR 213, GLU 214, SER 212, GLN 215 | conventional hydrogen bond, Carbon hydrogen bond, Pi-Pi Stacked, Alkyl, Pi-Alkyl |
|  | Nimbionone | -6.3 | 28.2 | GLU 167, ASP 164, MET 208, PRO 247, THR 301, TYR 268, TYR 264, PRO 248, GLY 163, LEU 162, LYS 157 | Van der waals, Carbon hydrogen bond, Conventional Hydrogen Bond hydrogen bond, Alkyl, Pi-Alkyl, Pi-Anion |
|  | Nimbolide | -7.3 | 5.35 | GLU 252, LYS 254, THR 257, GLU 214, TYR 213, TYR 305, SER 212, TYR 251 | Van der waals, conventional hydrogen bond, Pi-Anion |
|  | Nimocinol | -6.8 | 12.3 | THR 231, LYS 218, GLY 219, VAL 188, TYR 233, ILE 314, PRO 316, LEU 317, GLU 318, LYS 315 | Van der waals, Conventional Hydrogen Bond, Alkyl, Pi-Alkyl |
|  | Quercetin 3,4-diglucoside | -8.2 | 1.2 | LYS 306, TYR 310, LYS 217, GLU 307, ASN 308, LYS 254, GLU 252, THR 257, TYR 213, TYR 251, SER 212, GLU 214, TYR 305, GLY 256, PHE 258, SER 278, THR 259 | Van der waals, Conventional hydrogen bond, Carbon hydrogen bond, Unfavorable donor-donor, Unfavorable Acceptor-Acceptor, Pi-Alkyl |
|  | Quercetin 3,7,4-triglucoside | -8.6 | 0.62 | SER 278, LYS 279, GLY 256, LYS 217, SER 309, TYR 310, GLU 307, ASN 308, LYS 306, GLU 214, TYR 213, TYR 305, LEU 211, SER 212, TYR 251, GLU 252, LYS 254, THR 257, THR 259, PHE 258 | Van der waals, conventional hydrogen bond, Carbon hydrogen bond, Pi-Anion,  Pi-Alkyl |
|  | Quercetin 3-glucoside | -7.7 | 2.8 | PRO 247, TYR 268, GLN 269, LEU 162, GLY 163, GLY 271, VAL 165, ASP 164, TYR 273, TYR 264, THR 301, ASN 267, PRO 248, GLY 266 | Van der waals, Conventional hydrogen bond, Carbon hydrogen bond, Unfavorable Acceptor-Acceptor, Pi Stacked Pi-Alkyl |
|  | Quercetin 7,4-diglucoside | -8.5 | 7.3 | GLU 252, THR 257, GLU 215, TYR 305, LYS 306, THR 259, PHE 258, GLY 256, SER 278, GLU 307, LYS 217, GLU 214, TYR 213, SER 212, TYR 251, LYS 254, LEU 253 | Van der waals, conventional hydrogen bond, Carbon hydrogen bond, Unfavorable donor-donor, Pi-Pi T-shaped, Pi-Anion |
|  | Quercetin | -7.1 | 7.5 | GLU 307, LYS 217, TYR 305, GLU 214, TYR 213, TYR 251, SER 212, THR 257, LYS 306 | Van der waals, conventional hydrogen bond, Unfavorable donor-donor, Pi-Anion, Pi-Pi T-shaped |
|  | Quercetin-4-glucoside | -8.2 | 1.2 | GLU 252, TYR 251, THR 257, TYR 305, LYS 306, GLU 307, LYS 217, GLU 214 | Conventional hydrogen bond, Carbon hydrogen bond, Unfavorable donor-donor, Unfavorable Acceptor-Acceptor, Pi-Anion, Pi-Donor Hydrogen Bond, Pi-Pi Stacked |
|  | Regorafenib | -7.0 | 8.8 | LYS 279, THR 277, GLN 122, THR 257, LYS 217, TYR 213, GLU 307, ASN 308, LYS 306, TYR 305, GLY 256, THR 259, PHE 259, SER 278 | Van der waals, conventional hydrogen bond, Carbon Hydrogen Bond, Halogen (Fluorine), Pi-Alkyl |
|  | Rutin | -7.7 | 2.8 | GLN 174, THR 75, PHE 69, THR 74, HIS 73, ASN 128, ASP 76, ASN 156, ARG 82, ALA 153, TYR 154, PHE 79, HIS 175 | Van der waals, conventional hydrogen bond, Unfavorable acceptor-acceptor, Unfavorable Donor-Donor, Pi-Pi Stacked, Pi-Pi T-shaped |
|  | Salannol acetate | -6.3 | 28.2 | ASN 156, ARG 82, PHE 79, ASP 76, THR 75, THR 74, PHE 69, HIS 73, GLN 174, HIS 175, TYR 154 | Conventional hydrogen bond, Unfavorable acceptor-acceptor Pi-Pi Stacked, Pi-Alkyl |
|  | s-propylcysteine | -3.4 | 3504 | TYR 268, TYR 264, TYR 273, ASP 164, GLY 163, LEU 162, GLY 271, CYS 270, GLN 269 | Van der waals, conventional hydrogen bond |
|  | Terpiene-4-ol | -4.6 | 476 | GLU 214, TYR 305, THR 257, TYR 251, PHE 258, LEU 253, VAL 303, GLU 252, LYS 254 | Van der waals, Alkyl, Pi-Alkyl |
|  | Thymol | -4.7 | 403 | TYR 268, TYR 264, THR 301, PRO 248, VAL 165, TYR 273, GLY 163, ASP 164 | Van der waals, conventional hydrogen bond, Alkyl, Pi-Anion, Pi-Sigma |
|  | Trans carveol | -4.8 | 342 | VAL 188, PRO 316, GLU 318, THR 231, TYR 233, GLY 219, LYS 218, ILE 314 | Van der waals, Alkyl, Pi-Alkyl |
|  | Verbenone | -4.9 | 289 | THR 231, TYR 233, ILE 314, VAL 188, LYS 218, PRO 316, LEU 317 | Van der waals, Alkyl, Pi-Alkyl |
|  | Zwiebelene | -4.0 | 1292 | GLU 214, TYR 251, SER 212, TYR 305, TYR 213, THR 257, PHE 258, LYS 254 | Van der waals, conventional hydrogen bond, Unfavorable acceptor-acceptor Alkyl, Pi-Sulfur |
| \*48 | Dexamethasone | -7.1 | 7.5 | ASN 146, LEU 87, ALA 145, ALA 144, GLU 143, TRP 93, PRO 96, TYR 95, GLY 142, LYS 94, LYS 91 | Van der waals, Conventional Hydrogen Bond, Unfavorable Donor-Donor, Halogen (Fluorine), Pi-Alkyl, Alkyl |

\*Used as standard

**Table 2: Docking score and the interactions of the natural compounds with 3CLpro**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **S/N** | **Ligands** | **Binding Affinity ΔG (Kcal/mol)** | **Inhibition Constant Ki (µM) 10-6** | **Interacting Amino acids** | **Bond Type** |
|  | 3-deacetylsalanin | -8.2 | 12 | TYR 237, LEU 286, ASP 197, THR 196, LYS 137, ARG 131, THR 199, TYR 239, LEU 287, LEU 272 | Van der waals,  Conventional hydrogen bond, P-Sigma, Alkyl |
|  | Alpha terpineol | -5.4 | 126.0 | ILE 106, VAL 104, SER 158, ASN 151, GLN 110, ARG 298 | Van der waals, conventional hydrogen bond, Alkyl |
|  | Apigenin | -8.5 | 0.7 | LEU 287, LEU 286, ASP 289 | Pi-Anion, Pi-Alkyl |
|  | Azadirachtin | -8.0 | 1.7 | LEU 286, ARG 131, LYS 137, ASP 197, GLU 288, ASP 289, VAL 204, LEU 287, THR 199, LEU 272, TYR 239, ASN 238, TYR 237 | Van der waals, conventional hydrogen bond, Alkyl |
|  | Azadironic acid | -9.3 | 0.2 | MET 276, TYR 239, LEU 287, TYR 237 | Conventional hydrogen bond, Alkyl, Pi-Alkyl |
|  | Bornyl acetate | -6.0 | 46.4 | VAL 104, GLN 110, ARG 298 | Conventional hydrogen bond, Alkyl |
|  | Buoebenone | -6.2 | 33.3 | LEU 287, TYR 239, TYR 237, LEU 272, LEU 286, ASN 238, THR 199 | Van der waals, Alkyl, Pi-Alkyl |
|  | Carvone | -5.2 | 176.0 | LEU 220, ASN 221, PHE 219, TRP 218, LEU 271, GLU 270, ASN 274, ARG 279 | Van der waals, Alkyl |
|  | Citral | -5.0 | 245.0 | LEU 287, TYR 239, LEU 286, LEU 272, TRY 237, THR 199, ASN 238 | Van der waals, conventional hydrogen bond, Alkyl, P-Alkyl |
|  | Citronellol | -5.5 | 107.0 | ARG 131, ILE 200, ASP, 289, THR 199, TYR 239, LEU 272, LEU 287, LEU 286 | Van der waals, conventional hydrogen bond, Alkyl, Pi-Alkyl |
|  | Copaene | -6.8 | 12.3 | TYR 239, LEU 287, MET 276, LEU 272, LEU 286, GLY 275, LEU 271 | Van der waals, Alkyl |
|  | Cryptone | -5.2 | 176.0 | LYS 90, LYS 88, VAL 35 | Alkyl |
|  | Cubebene | -6.6 | 17.1 | LEU 287, LEU 286, TYR 239, TYR 237, LEU 272, MET 276 | Alkyl, Pi-Alkyl |
|  | Cuminal | -5.8 | 64.8 | THR 199, GLY 275, LEU 286, LEU 271, MET 276, ALA 285, LEU 287, LEU 272, TYR 239 | Van der waals, Pi-Donor Hydrogen Bond, Alkyl, Pi-Alkyl |
|  | Cycloallin | -5.6 | 90.3 | LYS 5, PHE 291, PHE 3, TRP 207, SER 284, GLU 288, LEU 282, ILE 281, GLY 283, ARG 4 | Van der waals, conventional hydrogen bond, carbon hydrogen bond, Unfavorable donor-donor |
|  | Decadienal | -4.3 | 784.0 | Van der waals, conventional hydrogen bond, Pi-Sigma, Alkyl, Pi-Alkyl | Van der waals, Conventional Hydrogen Bond, Pi-Sigma, Alkyl, Pi-Alkyl |
|  | Gamma-s-propyl-cysteine | -5.7 | 76.5 | LEU 286, THR 199, TYR 237, TRY 239, ASP 289, LEU 287 | Van der waals, Conventional Hydrogen Bond, Alkyl |
|  | Isohamnetin 3,4-diglucoside | -10.1 | 0.05 | LEU 287, LEU 286, GLU 290, LYS 137, ASP 289, THR 199, TYR 237, ARG 131, ASN 238, ASP 197, MET 276, ALA 285 | Van der waals, conventional hydrogen bond, carbon hydrogen bond, Unfavorable donor-donor, Pi-Anion, Pi-Alkyl |
|  | Isorhamnetin 4-glucoside | -9.5 | 0.1 | LEU 271, LEU 272, THR 199, ASP 289, GLU 290, LYS 5, GLU 288, LEU 286, TYR 239, LEU 287 | Van der waals, conventional hydrogen bond, Pi-Anion, Pi-Sigma |
|  | Isorhamnetin | -8.0 | 1.7 | ASP 289, GLU 288, LYS 5, GLU 290, LYS 137, ARG 131, THR 199, LEU 272, TYR 239, LEU 287 | Van der waals, conventional hydrogen bond, Pi-Anion, Pi-Alkyl |
|  | Isovallinin | -5.1 | 207.0 | ALA 285, LEU 286, LEU 287, TYR 239, LEU 271, LEU 272, GLY 275, MET 276 | Van der waals, Carbon Hydrogen Bond, Pi-Alkyl |
|  | Kaempferol-3-O-rutinside | -10.6 | 0.02 | LEU 287, ARG 131, ASP 289, GLU 290, LYS 137, TYR 239, LEU 272, ASP 197, ASN 238 | Van der waals, Conventional Hydrogen Bond, Pi-Pi T-shaped, Alkyl, Pi-Alkyl |
|  | Luteolin | -8.6 | 0.6 | LEU 287, TYR 239, GLU 290, ASP 289, ARG 131, THR 199, LEU 286, TYR 237, ASN 238, LEU 272 | Van der waals, Conventional Hydrogen Bond, Pi=-Donor Hydrogen Bond, Pi-Pi T-shaped, Pi-Alkyl |
|  | Meliacinin | -8.6 | 0.6 | TYR 237, LEU 272, ASN 277, GLY 278, ALA 285, LEU 287, GLY 275, MET 276, TYR 239, LEU 286, THR 199 | Van der waals, Alkyl, Pi-Alkyl |
|  | Methin | -4.1 | 1094.0 | PRO 108, PRO 132, GLU 240, HIS 246, VAL 202, GLY 109, ILE 200 | Van der waals, Conventional Hydrogen Bond, Pi-Sulfur |
|  | Methychavicol | -5.5 | 107.0 | GLY 275, LEU 271, MET 276, LEU 272, TYR 239, LEU 287, LEU 286, THR 199, TYR 237 | Van der waals, Carbon Hydrogen Bond, Pi-Donor Hydrogen Bond, Alkyl, Pi-Alkyl |
|  | Myrtenal | -5.5 | 107.0 | THR 199, TYR 239, LEU 272, LEU 286, MET 276, LEU 287, GLY 275, ALA 285 | Van deer waals, Conventional Hydrogen Bond, Alkyl |
|  | Nimbanal | -8.9 | 0.4 | LEU 272, LEU 287, LEU 286, ASP 289, THR 199, ARG 131, LYS 137, THR 198, ASP 197, THR 196, ASN 238, TYR 239, MET 276 | Van der waals, Conventional Hydrogen Bond, Carbon Hydrogen Bond, Unfavorable Acceptor-Acceptor, Pi-sigma, Pi-Sulfur, Alkyl, Pi-Alkyl |
|  | Nimbionol | -8.0 | 1.7 | ILE 152, ASP 153, SER 158, CYS 160, VAL 104, GLN 110, ILE 106, PHE 8, ASN 151, THR 111, ARG 298 | Van der waals, Conventional Hydrogen Bond, Carbon Hydrogen Bond, Alkyl |
|  | Nimbionone | -8.3 | 1.0 | LEU 286, LEU 287, TYR 239, THR 199, ASP 289, GLU 288, GLU 290 | Van der waals, Conventional Hydrogen Bond, Pi-Sigma, Alkyl, Pi-Alkyl |
|  | Nimbolide | -9.3 | 0.2 | SER 158, VAL 104, ARG 105, GLN 107, ILE 106, GLN 110, ASN 151, PHE 294, ILE 152, ARG 298, ASP 153 | Van der waals, Conventional Hydrogen Bond, Carbon Hydrogen Bond, Pi-Sigma, Alkyl |
|  | Nimocinol | -8.6 | 0.6 | TYR 237, LEU 272, MET 276, LEU 286, LEU 287, TYR 239, TYR 237 | Van der waals, Alkyl, Pi-Alkyl |
|  | Quercetin 3,4-diglucoside | -10.1 | 0.05 | ASN 238, TYR 237, TYR 239, THR 198, THR 199, LEU 272, LEU 287, MET 276, LEU 271, GLY 275, LEU 286, ASP 197, GLU 288, ASP 289, LYS 5, GLU 290, ARG 131, LYS 137 | Van der waals, Conventional Hydrogen Bond, Unfavorable Donor-Donor, Pi-Sigma, Pi-Sulfur, Pi-Alkyl |
|  | Quercetin 3,7,4-triglucoside | -10.8 | 0.02 | LYS 5, LEU 287, GLU 288, TYR 239, LEU 286, LEU 272, GLY 275, LEU 271, MET 276, ALA 285, TYR 237, THR 199, THR 198, ASN 238, LYS 137, ASP 197, ASP 289, ARG 131, CYS 128, GLU 290 | Van der waals, Conventional Hydrogen Bond, Unfavorable Donor-Donor, Pi-Cation, Pi-Anion, Pi-Donor Hydrogen Bond, Pi-Alkyl |
|  | Quercetin 3-glucoside | -9.6 | 0.1 | LYS 5, ASN 238, TYR 237, THR 199, THR 198, THR 196, ASP 197, TYR 239, LEU 286, LEU 287, ARG 131, ASP 289, LYS 137, GLU 290, GLU 288 | Van der waals, Conventional Hydrogen Bond, Pi-Anion, Pi-Alkyl |
|  | Quercetin 7,4-diglucoside | -10.0 | 0.06 | THR 199, ARG 131, THR 198, ASP 197, ASP 289, LYS 137, GLU 290, CYS 128, GLN 127, TYR 126, ARG 4, TRP 207, PHE 291, SER 284, LEU 282, GLY 283, LEU 286, LEU 287 | Van der waals, Conventional Hydrogen Bond, Carbon Hydrogen Bond, Pi-Cation, Pi-Anion, Pi-Alkyl |
|  | Quercetin | 8.4 | 0.9 | GLU 290, GLU 288, ASP 289, TYR 239, LEU 287, LEU 286 | Van der waals, Conventional Hydrogen Bond, Pi-Donor Hydrogen Bond, Pi-Sigma, Pi-Alkyl |
|  | Quercetin-4-glucoside | -9.7 | 0.1 | LYS 137, CYS 128, LYS 5, GLU 288, ARG 131, ASP 289, THR 199, TYR 237, TYR 239, LEU 272, MET 276, LEU 287, LEU 286, GLU 290 | Van der waals, Conventional Hydrogen Bond, Pi-Donor Hydrogen Bond, Pi-Alkyl |
|  | Regorafenib | -9.7 | 0.1 | GLU 288, ARG 131, ASP 289, LEU 287, LEU 271, LEU 272, TYR 237, TYR 239, THR 199 | Conventional Hydrogen Bond, Halogen (Fluorine), Pi-Cation, Pi-Anion, Pi-Donor Hydrogen Bond, Alkyl, Pi-alkyl |
|  | Rutin | -10.4 | 0.03 | ASN 238, LYS 236, MET 276, LEU 287, LEU 286, ASP 289, GLU 290, ARG 131 | Van der waals, Conventional Hydrogen Bond, Carbon Hydrogen Bond, Unfavorable Accepor-Acceptor, Pi-Sulfur, Pi-Alkyl |
|  | Salannol acetate | -7.8 | 2.3 | GLU 288, LYS 137, ASP 197, ARG 131, TYR 237, TYR 239, LEU 286, THR 199, LEU 287, ASP 289 | Van der waals, Conventional Hydrogen Bonds, Carbon Hydrogen Bond, Unfavorable Acceptor-Acceptor,, Pi-Anion, Alkyl |
|  | s-propylcysteine | -3.9 | 1526.0 | THR 199, LEU 287, LEU 286, ASP 289, ARG 131, LYS 137, THR 198, ASP 197 | Van der waals, Conventional Hydrogen Bond, Alkyl |
|  | Terpiene-4-ol | -5.3 | 149.0 | LEU 286, THR 199 | Conventional Hydrogen Bond, Alkyl |
|  | Thymol | -5.8 | 64.8 | LYS 90, LYS 88, VAL 35 | Conventional Hydrogen Bond, Pi-Cation, Pi-Sigma, Alkyl, Pi-Alkyl |
|  | Trans carveol | -5.7 | 76.5 | THR 198, THR 199, ASP 197, LYS 137, LEU 286, GLU 288, LEU 287, ARG 131, ASP 289 | Van der waals, Conventional Hydrogen Bond, Unfavorable Acceptor-Acceptor, Alkyl |
|  | Verbenone | -6.1 | 39.3 | THR 199, LEU 287, LEU 286, GLU 288, ASP 289, ARG 131 | Van der waals, Conventional Hydrogen Bond, Alkyl |
|  | Zwiebelene | -4.9 | 289.0 | ARG 131, LEU 286 | Conventional Hydrogen Bond, Alkyl |
| \*48 | Dexamethasone | -9.4 | 0.16 | TYR 237, THR 199, GLU 290, ASP 289, ARG 131, ASP 197, LYS 137, GLU 288, LEU 286, LEU 287, TYR 239, LEU 272 | Van der waals,  Conventional hydrogen bond, Alkyl |

\*Used as standard

**Table 3: Docking score and the interactions of the natural compounds with RdRp**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **S/N** | **Ligands** | **Binding Affinity ΔG (Kcal/mol)** | **Inhibition Constant Ki (µM) 10-6** | **Interacting Amino acids** | **Bond Type** |
|  | 3-deacetylsalanin | -6.6 | 17.1 | ASN 705, HIS 133, TYR 728,LEU 240, LEU 708, SER 709, THR 710, ASP 711, ASP 208, ASP 126, ALA 125, TYR 129 | Van der waals, carbon hydrogen bond, Pi-Cation, Pi-Pi T-Shaped, Alkyl, Pi-Alkyl |
|  | Alpha terpineol | -5.4 | 126.0 | TYR 728 | Pi-Sigma, Pi-Alkyl |
|  | Apigenin | -7.6 | 3.3 | ASP 618, ASP 760, ALA 762, ASP 761, PHE 812, TRP 800, GLY 616, TRP 617, GLU 811, HIS 810, LYS 798, ALA 797 | Van der waals, conventional hydrogen bonds, Pi-Anion, Pi-Alkyl |
|  | Azadirachtin | -7.2 | 6.3 | ALA 383, ALA 399, VAL 398, SER 397, LEU 387, PHE 396, LEU 270, PHE 326, VAL 675, PRO 328, THR 324, GLY 327, SER 325, LEU 329, VAL 330, LEU 271, TYR 273 | Van der waals, conventional hydrogen bond, carbon hydrogen bond, Alkyl |
|  | Azadironic acid | -9.0 | 0.3 | ASP 126, ALA 125, LEU 207, THR 206, ASP 208,LEU 240, LEU 708, TYR 732, TYR 728, GLN 468, ASP 465, ARG 132, ASN 705, VAL 704, SER 709, HIS 133, TYR 129 | Van der waals, conventional hydrogen bond, Alkyl, Pi-Alkyl |
|  | Bornyl acetate | -5.4 | 126.0 | ALA 685, LYS 577, ARG 569, TYR 689, LEU 576, ASN 496, ASN 497 | Van der waals, conventional hydrogen bond, Alkyl, Pi-Alkyl |
|  | Buoebenone | -6.5 | 20.2 | MET 666, VAL 398, PRO 378, GLY 327, PRO 328, VAL 341, VAL 330, ALA 383, ALA 382, ALA 379 | Van der waals, Alkyl |
|  | Carvone | -5.3 | 149.0 | MET 666, ALA 382, PRO 328, PRO 378, VAL 398, VAL 330, VAL 341, ALA 383, ALA 379 | Alkyl |
|  | Citral | -5.0 | 245.0 | LEU 371, ALA 375, TRP 509, LEU 514, SER 518 | conventional hydrogen bond, Carbon hydrogen bond, Pi-Sigma, Alkyl, Pi-Alkyl |
|  | Citronellol | -4.8 | 342.0 | TYR 515, LEU 514, TRP 509, PHE 506, LEU 372, PHE 368, LEU 371, ALA 375 | Van der waals, Pi-Sigma, Alkyl, Pi-Alkyl |
|  | Copaene | -6.7 | 14.5 | LEU 371, ALA 375, LEU 372, PHE 368, TYR 515, PHE 506, LEU 514, TRP 509 | Alkyl, Pi-Alkyl |
|  | Cryptone | -5.3 | 149.0 | TYR 129, ARG 132, LEU 240, ALA 125, LEU 207, VAL 128, HIS 133 | Van der waals, Alkyl, Pi-Alkyl |
|  | Cubebene | -6.1 | 39.3 | TYR 732, ASN 705, GLN 468, ARG 132, TYR 129, LEU 708, LEU 240, HIS 133, VAL 128, TYR 728, SER 709, | Van der waals, Alkyl, Pi-Alkyl |
|  | Cuminal | -5.4 | 126.0 | TRP 509, PHE 368, ALA 375, PHE 506, TYR 515, LEU 514 | Van der waals, Pi-Sigma, Pi-Pi Stacked Alkyl, Pi-Alkyl |
|  | Cycloallin | -5.8 | 64.8 | GLU 811, TRP 800, GLY 616, PHE 812, ALA 762, VAL 763, TRP 617, ASP 761, ASP 760, ASP 618, LYS 798 | Van der waals, conventional hydrogen bond |
|  | Decadienal | -4.7 | 403.0 | TYR 530, SER 367, LEU 527, LYS 369, ALA 526, VAL 373, ILE 333, ASN 360, VAL 359, TYR 374, ASP 358, GLU 370 | Van der waals, conventional hydrogen bond, Alkyl, Pi-Alkyl |
|  | Gamma-s-propyl-cysteine | -4.8 | 342.0 | SER 682, SER 681, LYS 676, GLU 665, VAL 667, TYR 456, MET 542, GLN 541, GLY 503, VAL 560, GLY 683, THR 540 | Van der waals, conventiona hydrogen bond, Unfavorable donor-donor |
|  | Isohamnetin 3,4-diglucoside | -8.4 | 0.9 | LEU 731, TYR 732, LEU 240, TYR 728, ASN 713, ARG 721, HIS 725, GLN 724, GLY 712, THR 710, ASP 711, SER 709, LEU 708, TYR 129, HIS 133, ASN 705 | Van der waals, conventional hydrogen bond, carbon hydrogen bond, Unfavorable donor-donor, Pi-Pi Stacked, Pi-Alkyl |
|  | Isorhamnetin 4-glucoside | -8.0 | 1.7 | LEU 240, HIS 133, ASP 711, GLY 712, GLN 724, LEU 708, THR 710 VAL 128 | conventional hydrogen bond, Carbon hydrogen bond, Pi-Sigma, Pi-Alkyl |
|  | Isorhamnetin | -6.7 | 14.5 | CYS 813, ASP 760, CYS 622, ASP 761, LYS 798, TRP 800, CYS 799, TRP 617, GLY 616, ASP 618, GLU 811, PHE 812, SER 814 | Van der waals, conventional hydrogen bond, Unfavorable donor-donor, Pi-Anion |
|  | Isovallinin | -5.3 | 149.0 | PRO 677, LYS 676, VAL 675, SER 664, GLY 327, TYR 346, HIS 347, PHE 348, PHE 326, ARG 349, PRO 323, PHE 396 | Van der waals, conventional hydrogen bond, Carbon hydrogen bond, Unfavorable donor-donor, Pi-Cation, Pi-Donor hydrogen donor, Pi-Sigma, Pi-Alkyl |
|  | Kaempferol-3-O-rutinside | -8.0 | 1.7 | HIS 725, GLN 724, LEU 708, SER 709, ASN 705, GLN 468, ARG 132, ASP 465, HIS 133, TYR 732, TRY 129, VAL 128, ALA 125, LEU 240, SER 236, LEU 207, TYR 728, THR 206, ASP 208 | Van der waals, conventional hydrogen bond, Pi-Alkyl |
|  | Luteolin | -7.7 | 2.8 | ALA 797, GLU 811, LYS 798, ASP 618, ASP 760, ALA 762, ASP 761, PHE 812, TRP 800, TRP 617, GLY 616, HIS 810 | Van der waals, conventional hydrogen bond, Pi-Anion, Pi-Alkyl |
|  | Meliacinin | -7.2 | 6.3 | ARG 349, PRO 323, PHE 396, PRO 677, THR 394, TYR 458, ARG 457, LEU 172, LEU 460, PRO 461 | conventional hydrogen bond, Alkyl, Pi-Alkyl |
|  | Methin | -4.2 | 926.0 | AP 618, LYS 798, TRP 800, GLY 616, TRP 617, ALA 762, ASP 761, CYS 813, PHE 812, GLU 811, SER 814 | Van der waals, conventional hydrogen bond, Unfavorable donor-donor |
|  | Methychavicol | -5.0 | 245.0 | HIS 133, TYR 732, ASN 705, LEU 708, ARG 132, LEU 240, ALA 125, TYR 129, VAL 128, LEU 207 | Van der waals, Carbon hydrogen bond, Pi-Cation, Pi-Pi T-shaped, Alkyl, Pi-Alkyl |
|  | Myrtenal | -5.5 | 107.0 | TRP 800, ASP 618, CYS 813, PHE 812, GLU 811, SER 814, ASP 761, TRP 617, ALA 762, GLY 616 | Van der waals, conventional hydrogen bond |
|  | Nimbanal | -7.3 | 5.4 | ARG 569, ASN 497, LYS 500, SER 682, ALA 688, TYR 689 | conventional hydrogen bond, Carbon hydrogen bond, Alkyl, Pi-Alkyl |
|  | Nimbionol | -6.8 | 12.3 | ASN 705, ARG 132, TYR 129, VAL 128, LEU 207, ALA 125, LEU 240, LEU 708, SER 709, HIS 133 | Van der waals, conventional hydrogen bond, Carbon hydrogen bond, Pi-Sigma, Alkyl, Pi-Alkyl |
|  | Nimbionone | -7.4 | 4.5 | TRP 509, PHE 368, TYR 515, LEU 372, PHE 506, ALA 375, LEU 371, TYR 374 | Van der waals, Pi-Pi Stacked, Alkyl, Pi-Alkyl |
|  | Nimbolide | -7.7 | 2.8 | PRO 677, VAL 675, PHE 326, PHE 396, ARG 349, PRO 323, PRO 461, LEU 460, THR 393, ARG 457 | Van der waals, conventional hydrogen bond, Pi-Cation, Pi-Donor Hydrogen Bond, Pi-Sigma, Pi-Pi Stacked, Alkyl |
|  | Nimocinol | -9.3 | 0.2 | HIS 133, ASN 705, ARG 132, TYR 129, VAL 128, ALA 125, LEU 207, THR 206, ASP 208, LEU 240, TYR 728, LEU 708, SER 709, TYR 732 | Van der waals, conventional hydrogen bond, Pi-Anion, Alkyl, Pi-Alkyl |
|  | Quercetin 3,4-diglucoside | -9.1 | 0.3 | ARG 132, LEU 240, GLU 729, HIS 725, GLY 712, GLN 724, THR 710, LEU 708, SER 709, ASP 208 LEU 207, THR 206, SER 236, ALA 125, TYR 728, VAL 128, TYR 129, HIS 133 | Van der waals, conventional hydrogen bond, Unfavorable donor-donor, Pi-Sigma, Pi-Alkyl |
|  | Quercetin 3,7,4-triglucoside | -8.8 | 0.4 | PRO 620, CYS 622, ASP 623, TYR 619, SER 759, ASN 691, SER 814, LYS 798, GLU811, GLY 616, TRP 617, ASP 761, ALA 762, TRP 800, ASP 618, LYS 621 | Van der waals, conventional hydrogen bond, Carbon hydrogen bond, Unfavorable donor-donor, Pi-Donor Hydrogen Bond |
|  | Quercetin 3-glucoside | -8.5 | 0.7 | CYS 813, SER 814, ASP 760, ASP 618 LYS 798, GLU 811, TRP 800, TRP 617, ALA 762, ASP 761, SER 759, ALA 688, LEU 758 | Van der waals, conventional hydrogen bond, Carbon hydrogen bond, Unfavorable Acceptor-Acceptor, Pi-Alkyl |
|  | Quercetin 7,4-diglucoside | -8.9 | 0.4 | THR 591, TRP 617, ALA 762, SER 814, ASP 761, LEU 758 | conventional hydrogen bond, Unfavorable donor-donor, Pi-Anion, Pi-Sigma, Pi-Alkyl |
|  | Quercetin | -7.4 | 4.5 | THR 324, LEU 271, HIS 355, ARG 331, TYR 273, VAL 330, LEU 329 | conventional hydrogen bond, , Pi-Sigma, Pi-Pi Stacked, Pi-Alkyl |
|  | Quercetin-4-glucoside | -8.1 | 1.4 | ARG 132, HIS 133, SER 709, LEU 708, GLY 712, ASP 711, ASN 713, HIS 725, GLN 724, TYR 728, ALA 125, LEU 207, TYR 129, LEU 240, VAL 128 | Van der waals, conventional hydrogen bond, Unfavorable donor-donor, Pi-Sigma, Pi-Alkyl |
|  | Regorafenib | -7.9 | 2.0 | ARG 249, LEU 460, ASN459, PRO 461, PRO 677, CYS 395, ARG 349, VAL 675, PHE 326, GLY 327, THR 324, PRO 323, PHE 396, TYR 458, PHE 165, ARG 457, PRO 169, LEU 172 | Van der waals, Carbon hydrogen bond, Halogen (Fluorine), Pi-Cation, Pi-Donor Hydrogen Bond, Pi-Sigma, Alkyl Pi-Alkyl |
|  | Rutin | -8.2 | 1.2 | CYS 622, ASP 760, SER 759, SER 814, ASP 761, GLU 811, TRP 800, LYS 798 | Conventional Hydrogen Bond, Pi-Donor Hydrogen Bond, Pi-Sulfur, Alkyl |
|  | Salannol acetate | -7.4 | 4.5 | GLN 724, LEU 708, HIS 725, TYR 728, LEU 240, HIS 133 | Conventional Hydrogen bond, Pi-Cation, Pi-Sigma, Pi-Pi T-shaped, Alkyl, Pi-Alkyl |
|  | s-propylcysteine | -3.7 | 2128.0 | GLU 811, GLY 616, TRP 800, TRP 617, ALA 762, ASP 761, ASP 760, ASP 618 | Van der waals, conventional hydrogen bond, Unfavorable donor-donor |
|  | Terpiene-4-ol | -5.2 | 176.0 | LEU 240, HIS 133 | Alkyl, Pi-Alkyl |
|  | Thymol | -5.3 | 149.0 | HIS 810, LYS 798, GLU 811, TRP 800, ASP 761, PHE 812, SER 814, CYS 813, GLY 616 | Van der waals, Unfavorable donor-donor, Unfavorable acceptor-acceptor, Pi-Anion, Alkyl |
|  | Trans carveol | -5.3 | 149.0 | LEU 708, TYR 732, GLN 468, ASN 705, ARG 132, LEU 240, TYR 129, VAL 128, HIS 133, SER 709, TYR 728 | Van der waals, conventional hydrogen bond, Alkyl, Pi-Alkyl |
|  | Verbenone | -5.8 | 64.8 | ARG 132, TYR 129, HIS 133, SER 709, LEU 240, LEU 708, TYR 732, TRY 728, ASN 705, GLN 468, ASP 465 | Van der waals, conventional hydrogen Alkyl , Pi-Alkyl |
|  | Zwiebelene | -4.7 | 403.0 | TRP 800 | Conventional hydrogen bond, Pi-Sulfur |
| \*48 | Dexamethasone | 7.3 | 5.4 | THR 710, GLY 712, SER 709, TYR 129, LEU 240, ALA 125 | Conventional Hydrogen Bond, Unfavorable Donor-Donor, Alkyl, Pi-Alkyl |

\*used as standard

**Table 4: Docking score and the interactions of the natural compounds with Host cell protease**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **S/N** | **Ligands** | **Binding Affinity ΔG (Kcal/mol)** | **Inhibition Constant Ki (µM)**  **10-6** | **Interacting Amino acids** | **Bond Type** |
|  | 3-deacetylsalanin | -6.4 | 23.9 | SER 408, ILE 404, LEU 96, PHE 401, GLU 91, LYS 405, GLY 87, ARG 84, ALA 98, ALA 86, THR 100, LUE 99, HIS 101, ALA 83, ARG 97 | Van der waals, conventional hydrogen bond, carbon hydrogen bond, Pi-Pi T-shaped, Alkyl, Pi-Alkyl |
|  | Alpha terpineol | -5.3 | 149.0 | PHE 66, PRO 53, PRO 50, LEU 51, TRP 73 | Van der waals, Alkyl, Pi-Alkyl |
|  | Apigenin | -7.6 | 3.25 | TYR 301, HIS 203, SER 376, SER 353, VAL 375, GLY 388, ALA 348, ASP 347, TRP 377, CYS 381, CYS 349, GLY 380, GLN 350, TYR 301 | Van der waals, conventional hydrogen bond, Carbon hydrogen bond, Amide-Pi Stacked  Pi-Alkyl |
|  | Azadirachtin | -7.0 | 8.8 | ASN 254, THR 379, TRP 377, CYS 349, VAL 375, GLY 378, SER 376, TYR 301, GLY 351, GLN 350, SER 353, HIS 186, GLN 305, LEU 187, HIS 203, PRO 206, ARG 208 | Van der waals, conventional hydrogen bond, Carbon hydrogen bond,  Pi-Alkyl |
|  | Azadironic acid | -7.2 | 6.3 | ALA 281, TYR 52, ARG 130. GLY 282, LEU 51, GLN 283, ILE 363, PRO 53, ALA 284, PRO 50, VAL 286, ASP 361, LYS 289 | Van der waals, conventional hydrogen bond, Alkyl  Pi-Alkyl |
|  | Bornyl acetate | -4.8 | 342.0 | HIS 203, GLY 351 | Conventional hydrogen bond, Pi-Alkyl |
|  | Buoebenone | -5.6 | 90.3 | PRO 50, TRP 73, PRO 53, TYR 52, PHE 66, LEU 51 | Van der waals, Alkyl, Pi-Alkyl |
|  | Carvone | -5.0 | 245.0 | PRO 53, PRO 50, LEU 51, PHE 66, TRP 73 | Van der waals, Alkyl, Pi-Alkyl |
|  | Citral | -4.5 | 562.0 | PHE 66, PRO 53, PRO 50, LEU 51, TRP 73 | Van der waals, conventional hydrogen bond, Alkyl,  Pi-Alkyl |
|  | Citronellol | -4.3 | 784.0 | PHE 66, TRP 73, PRO 53, GLU 49, LEU 51, PRO 50 | Van der waals, Unfavorable donor-donor,  Pi-Sigma, Alkyl, Pi-Alkyl |
|  | Copaene | -5.9 | 54.8 | PRO 50, LEU 51, TRP 73, PHE 66, TYR 52, PRO 53 | Van der waals, conventional hydrogen Pi-Sigma, Alkyl,  Pi-Alkyl |
|  | Cryptone | -4.7 | 403.0 | PRO 53, PRO 50, LEU 51, TRP 73, PHE 66 | Van der waals, Alkyl, Pi-Alkyl |
|  | Cubebene | -5.9 | 54.8 | GLU 49, PRO 53, PHE 66, TRP 73, PRO 50, LEU 51 | Van der waals, Pi-Sigma, Alkyl,  Pi-Alkyl |
|  | Cuminal | -5.4 | 126.0 | LEU 51, TRP 73, PHE 66, PRO 53 | Pi-Pi Stacked, Alkyl, Pi-Alkyl |
|  | Cycloallin | -4.8 | 342.0 | VAL 375, CYS 349, ASP 352, GLN 350, TYR 301, HIS 203, SER 376, TRP 377, SER 353 | Van der waals, conventional hydrogen bond,  Pi-Alkyl |
|  | Decadienal | -4.1 | 1095.0 | PRO 50, LEU 51, TRP 73, PHE 66, PRO 53 | Van der waals |
|  | Gamma-s-propyl-cysteine | -4.4 | 664.0 | GLY 87, ARG 84, LEU 96 | conventional hydrogen bond, Carbon hydrogen bond, |
|  | Isohamnetin 3,4-diglucoside | -8.0 | 1.7 | PRO 206, ASN 250, PRO 245, THR 379, TYR 301, GLY 388, GLY 378, GLY 380, VAL 375, ALA 348, ASP 347, CYS 381, CYS 349, GLN 350, TRP 377, GLY 351, SER 353, SER 376, HIS 203 | Van der waals, conventional hydrogen bond, Carbon hydrogen bond, Unfavorable donor-donor,  Unfavorable acceptor-acceptor, Pi-Cation, Pi-pi Stacked |
|  | Isorhamnetin 4-glucoside | -8.1 | 1.4 | PRO 206, ASN 250, GLY 380, GLY 378, HIS 203 | conventional hydrogen bond, Pi-Cation, Pi-Pi Stacked,  Pi-Alkyl |
|  | Isorhamnetin | -6.6 | 17.1 | HIS 203, CYS 381 | Pi-Cation, Pi-Sulfur, Pi-Pi Stacked |
|  | Isovallinin | -5.5 | 107.0 | SER 376, SER 353, HIS 203, TYR 301, GLY 380, CYS 349, GLY 378, CYS 381, ASP 347, ALA 348, GLY 388, VAL 375, TRP 377 | Van der waals, conventional hydrogen bond, Carbon hydrogen bond |
|  | Kaempferol-3-O-rutinside | -8.2 | 1.2 | TYR 243, PRO 206, ARG 208, ASN 250, GLY 378, CYS 381, GLN 350, HIS 203, SER 353, LEU 187 | Van der waals, conventional hydrogen bond, Pi-Cation, Pi-Pi T-shaped |
|  | Luteolin | -7.1 | 7.5 | TYR 301, GLN 350, HIS 203, SER 353, ALA 348, SER 376, CYS 381, VAL 375, VAL 389, GLY 388, ASP 347, TRP 377, GLY 378, CYS 349, GLY 380 | Van der waals, conventional hydrogen bond, Amide-Pi Stacked,  Pi-Alkyl |
|  | Meliacinin | -6.5 | 20.2 | GLN 283, VAL 286, ALA 284, PHE 66, TRP 73, LEU 51, PRO 53, GLY 282, PRO 50, TYR 52, ILE 363 | Van der waals, conventional hydrogen bond, Alkyl,  Pi-Alkyl |
|  | Methin | -4.3 | 784.0 | CYS 381, ALA 382, ASP 347, ALA 348, VAL 389, GLY 388, SER 376, TRP 377, VAL 375, SER 353, GLN 350, TYR 301, CYS 349, GLY 378, GLY 380 | Van der waals, conventional hydrogen bond, Carbon hydrogen bond, |
|  | Methychavicol | -4.9 | 289.0 | PRO 53, PHE 66, LEU 51, TRP 73 | Van der waals, Pi-Pi Stacked, Alkyl, Pi-Alkyl |
|  | Myrtenal | -5.4 | 126.0 | ALA 98, ARG 84, GLY 87, LYS 405, ILE 404, LEU 96, ARG 97, PHE 401, GLU 91 | Van der waals, conventional hydrogen bond, Carbon hydrogen bond, Alkyl,  Pi-Alkyl |
|  | Nimbanal | -7.6 | 3.25 | ASN 250, ARG 208, PRO 206, GLY 351, GLN 350, HIS 203, SER 353, TYR 301, GLY 378, TRP 377, TRY 243, SER 376, PRO 245, ASP 257, ASN 254 | Van der waals, conventional hydrogen bond, Carbon hydrogen bond, Alkyl,  Pi-Alkyl |
|  | Nimbionol | -6.9 | 10.4 | ARG 397, GLU 398, TRP 399, PHE 396, ASP 395, ARG 130, GLY 282, ALA 280, ALA 281, SER 394, GLN 283, LYS 392, ALA 284 | Van der waals, conventional hydrogen bond, Carbon hydrogen bond |
|  | Nimbionone | -7.0 | 8.8 | PRO 53, PRO 50, PHE 66, LEU 51, ARG 365, TRP 73, GLY 71 | Van der waals, Carbon hydrogen bond, Unfavorable donor-donor,  Pi-Sigma, Pi-Pi Stacked, Alkyl, Pi-Alkyl |
|  | Nimbolide | -7.3 | 5.4 | GLN 350, HIS 186, GLN 305, ALA 185, TYR 182, ASN 209, ARG 208, LEU 187, TRP 215, PRO 206, CYS 204, HIS 203, CYS 188, SER 353, GLY 351, | Van der waals, conventional hydrogen bond, Alkyl,  Pi-Alkyl |
|  | Nimocinol | -6.8 | 12.3 | GLY 378, GLN 350, GLY 351, SER 353, TYR 301, HIS 203, TRP 377. SER 376, TYR 243, ASN 254, PRO 245 | Van der waals, Pi-Cation, Pi-Sigma, Pi-Pi T-shaped, Pi-Alkyl |
|  | Quercetin 3,4-diglucoside | -7.9 | 2.0 | CYS 381, CYS 349, TYR 301, CYS 188, GLY 378, TRP 377, SER 376, HIS 203, SER 353, GLY 351, ASN 209, PRO 206, ARG 208, HIS 186, ALA 185, GLN 304, ASN 298, GLN 305, LEU 187,  GLN 350, CYS 188 | Van der waals, conventional hydrogen bond, Carbon hydrogen bond, Unfavorable donor-donor,  Pi-Sulfur, Pi-Alkyl |
|  | Quercetin 3,7,4-triglucoside | -7.8 | 2.3 | TRP 377, GLY 378, TYR 301, TRP 215, CYS 304, ASN 209, HIS 203, CYS 188, PHE 205, PRO 206, ARG 208, HIS 186, ALA 185, LEU 187, TYR 302, GLN 304, GLY 303, ASP 352, CYS 349, SER 376, VAL 375  ASN 298, GLY 351, GLN 350, SER 353 | Van der waals, conventional hydrogen bond, Carbon hydrogen bond, Unfavorable donor-donor,  Pi-Sigma, Pi-Alkyl |
|  | Quercetin 3-glucoside | -8.0 | 1.7 | HIS 203, GLY 351, TYR 301, GLY 380, GLY 378, CYS 381, CYS 349, ASP 352, TRP 377, ALA 348, VAL 375, ASN 298, SER 353, GLN 305,GLN 350, HIS 186, ALA 185, LEU 187 | Van der waals, conventional hydrogen bond, Unfavorable donor-donor, Pi-Cation, Amide-Pi Stacked,  Pi-Alkyl |
|  | Quercetin 7,4-diglucoside | -8.3 | 1.0 | PRO 206, ASN 209, ARG 208, LEU 187, CYS 188, HIS 203, SER 353, SER 376, TYR 301, GLY 380, CYS 381, CYS 349, ALA 348, VAL 375, GLY 378, TRP 377, VAL 389, GLY 388, ASP 347, ALA 185, TYR 182, GLN 350 | Van der waals, conventional hydrogen bond, Carbon hydrogen bond, Pi-Cation, Pi-Sulfur,  Pi-Alkyl |
|  | Quercetin | -8.0 | 1.7 | CYS 381, CYS 349, TRP 377, ASP 347, ALA 348, GLY 380, GLY 378, GLN 350, HIS 203 | Van der waals, conventional hydrogen bond, Carbon hydrogen bond, Unfavorable donor-donor,  Pi-Cation, Pi-Pi Stacked, Amide-Pi Stacked,  Pi-Alkyl |
|  | Quercetin-4-glucoside | -7.9 | 2.0 | HIS 203, CYS 381 | Conventional hydrogen bond, Pi-Cation, Pi-Pi Stacked |
|  | Regorafenib | -7.7 | 2.8 | ASN 209, ARG 208, TYR 182, ASP 183, ALA 185, LEU 187, HIS 186, CYS 381, CYS 349, TYR 301, GLN 350, GLY 380, GLY 378, TRP 377, SER 353, GLY 351, HIS 203 | Van der waals, conventional hydrogen bond, Carbon hydrogen bond, Halogen (Fluorine),  Pi-Alkyl |
|  | Rutin | -8.2 | 1.2 | ARG 208, PRO 206, PRO 245, ASN 250, HIS 203, GLY 351, GLN 350, GLY 378, TYR 301 | Van der waals, conventional hydrogen bond, Unfavorable donor-donor, Pi-Cation, Pi-Pi T-shaped,  Pi-Alkyl |
|  | Salannol acetate | -7.9 | 2.0 | TYR 243, ASN 254, GLU 253, SER 251, THR 379, GLN 350, GLY 378, CYS 381, GLY 380, TYR 301, CYS 349, ALA 348, ASP 347, GLY 388, VAL 389, VAL 375, SER 376, TRP 377, HIS 203, SER 353 | Van der waals, conventional hydrogen bond, Carbon hydrogen bond, Amide-Pi Stacked, Alkyl,  Pi-Alkyl |
|  | s-propylcysteine | -3.4 | 3504.0 | ASP 60, ASP 152, ARG 368, PHE 95, VAL 56, CYS 150, ILE 149, ALA 61, SER 57, SER 58, ALA 59 | Van der waals, conventional hydrogen bond, Alkyl,  Pi-Alkyl |
|  | Terpiene-4-ol | -5.0 | 245.0 | PHE 66, TRP 73, PRO 53, LEU 51, PRO 50 | Van der waals, Alkyl,  Pi-Alkyl |
|  | Thymol | -5.5 | 107.0 | SER 353, GLN 350, TYR 301, THR 379, GLY 380, GLY 378, CYS 381, CYS 349, VAL 375,  CYS 349, VAL 389, ALA 348, ASP 347, GLY 388, TRP 377 | Van der waals, conventional hydrogen bond, Amide-Pi Stacked, Alkyl,  Pi-Alkyl |
|  | Trans carveol | -5.0 | 245.0 | ALA 284, PRO 50, LEU 51, PRO 53, ALA 381. GLY 282, TYR 52. GLN 283, ILE 363 | Van der waals, conventional hydrogen bond, Alkyl,  Pi-Alkyl |
|  | Verbenone | -5.5 | 107.0 | LYS 405, ILE 404, LEU 96, ARG 97, PHE 401, ARG 84, GLU 91, GLY 87, ALA 98 | Van der waals, Alkyl,  Pi-Alkyl |
|  | Zwiebelene | -4.2 | 926.0 | ARG 368, PHE 95, CYS 150, ILE 149, ALA 148, ALA 61, VAL 56, ASP 152, SER 58 | Van der waals, conventional hydrogen bond, Alkyl |
| \*48 | Dexamethasone | 7.3 | 5.4 | GLY 378, HIS 203, SER 353, SER 376 | Conventional Hydrogen Bond, Pi-Alkyl |

\* used as standard

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Query** | **DILI** | **Cyto- toxicity** | **HLM** | **Cyp1A2 Inhibitor** | **Cyp3A4 Inhibitor** | **Cyp2D6 Inhibitor** | **Cyp2C9 Inhibitor** | **Cyp2C19 Inhibitor** | **BBB** | **P-gp Inhibitor** | **P-gp Substrate** | **hERG Blocker** | **MMP** | **AMES** | **MRTD**  **(mg/day)** |
| 3-deacetylsalanin | Yes | No | Yes | No | Yes | No | No | No | No | Yes | Yes | No | No | No | 182 |
| Apigenin | No | No | Yes | Yes | Yes | No | No | Yes | No | No | No | No | Yes | No | 1567 |
| Azadironic acid | No | No | Yes | No | No | No | No | No | No | No | Yes | No | No | No | 257 |
| Azadirachtin | Yes | No | Yes | No | No | No | No | No | No | Yes | Yes | No | No | No | 141 |
| Cubebene | Yes | No | Yes | No | No | No | No | No | No | Yes | Yes | No | No | No | 55 |
| Buoebenone | No | No | Yes | No | No | No | No | No | No | Yes | No | No | No | No | 313 |
| Bornyl acetate | Yes | No | Yes | No | No | No | No | No | Yes | Yes | No | No | No | No | 22 |
| Copaene | Yes | No | Yes | No | No | No | No | No | No | No | Yes | No | No | No | 442 |
| Isohamnetin 3,4-diglucoside | No | No | Yes | No | No | No | No | No | No | No | No | No | No | Yes | 631 |
| Isorhamnetin 4-glucoside | No | No | Yes | No | No | No | No | No | No | Yes | Yes | No | No | Yes | 481 |
| Isorhamnetin | No | No | Yes | Yes | No | No | Yes | No | No | Yes | Yes | No | Yes | Yes | 393 |
| Kaempferol-3-O-rutinside | Yes | No | Yes | No | No | No | No | No | No | No | Yes | No | No | No | 584 |
| Luteolin | No | No | Yes | Yes | No | No | No | No | No | No | No | No | Yes | No | 1475 |
| Meliacinin | Yes | No | Yes | No | No | No | No | No | No | Yes | Yes | No | No | No | 79 |
| Nimbanal | Yes | No | Yes | No | Yes | No | No | No | No | Yes | Yes | No | No | No | 168 |
| Nimbionone | No | No | Yes | No | No | No | No | No | No | No | No | No | No | No | 46 |
| Nimbolide | No | No | Yes | No | Yes | No | No | No | No | Yes | Yes | No | No | No | 157 |
| Nimbionol | No | No | Yes | No | No | No | No | No | No | No | No | No | No | No | 116 |
| Quercetin 3,4-diglucoside | No | No | Yes | No | No | No | No | No | No | No | Yes | No | No | Yes | 667 |
| Quercetin 3,7,4-triglucoside | No | No | Yes | No | No | No | No | No | No | No | No | No | No | Yes | 867 |
| Nimocinol | No | No | Yes | No | No | No | No | No | No | Yes | Yes | No | No | No | 107 |
| Quercetin 3-glucoside | No | No | Yes | No | No | No | No | No | No | No | Yes | No | No | Yes | 703 |
| Quercetin | No | No | Yes | Yes | No | No | Yes | No | No | No | Yes | No | Yes | Yes | 1694 |
| Quercetin 7,4-diglucoside | No | No | Yes | No | No | No | No | No | No | No | No | No | No | Yes | 689 |
| Regorafenib | Yes | Yes | Yes | No | No | No | No | No | No | Yes | Yes | Yes | Yes | No | 242 |
| Rutin | Yes | No | Yes | No | No | No | No | No | No | No | Yes | No | No | Yes | 1200 |
| Salannol acetate | Yes | No | Yes | No | Yes | No | No | No | No | Yes | Yes | No | No | No | 237 |
| Verbenone | Yes | Yes | Yes | No | No | No | No | No | No | Yes | No | No | No | No | 14 |
| \*Dexamethasone | No | No | Yes | No | No | No | No | No | No | No | Yes | No | No | No | 8.4 |

**Table 5: ADMET Profile of the screened compound**

**Table 6: Classification of compounds according to the plant source and their structure**

|  |  |  |  |
| --- | --- | --- | --- |
| **Compound source** | **Compound name** | **Chemical ID** | **Compound structure** |
| ***A.indica*** | Meliacinin | [15885442](https://pubchem.ncbi.nlm.nih.gov/compound/15885442) | ChemSpider 2D Image | Meliacinin | C31H44O6 |
|  | Nimbanal | [14194023](https://pubchem.ncbi.nlm.nih.gov/compound/14194023) | ChemSpider 2D Image | Nimbanal | C29H34O8 |
|  | Nimbionol | [189704](https://pubchem.ncbi.nlm.nih.gov/compound/189704) | 2D chemical structure of 119875-24-0 |
|  | Nimbionone | [189706](https://pubchem.ncbi.nlm.nih.gov/compound/189706) | ChemSpider 2D Image | (10xi)-12-Hydroxy-13-methoxypodocarpa-8(14),9(11),12-triene-3,7-dione | C18H22O4 |
|  | Nimbolide | [100017](https://pubchem.ncbi.nlm.nih.gov/compound/100017) | ChemSpider 2D Image | GY2370000 | C27H30O7 |
|  | Nimocinol | [178770](https://pubchem.ncbi.nlm.nih.gov/compound/178770) | 2D chemical structure of 95260-96-1 |
|  | Quercetin | [5280343](https://pubchem.ncbi.nlm.nih.gov/compound/5280343) | InChI=1/C15H10O7/c16-7-4-10(19)12-11(5-7)22-15(14(21)13(12)20)6-1-2-8(17)9(18)3-6/h1-5,16-19,21H |
|  | Regorafenib | [11167602](https://pubchem.ncbi.nlm.nih.gov/compound/11167602) | ChemSpider 2D Image | Regorafenib | C21H15ClF4N4O3 |
|  | Salannol acetate | [14194026](https://pubchem.ncbi.nlm.nih.gov/compound/14194026) | CID:14194026 | IMPPAT: Indian Medicinal Plants, Phytochemistry And ... |
|  | 3-deacetylsalanin | 14458886 | 3-Deacetylsalannin.png |
|  | Azadirachtin | [5281303](https://pubchem.ncbi.nlm.nih.gov/compound/5281303) | ChemSpider 2D Image | Azadirachtin | C35H44O16 |
|  | Azadironic acid | [15885443](https://pubchem.ncbi.nlm.nih.gov/compound/15885443) | ChemSpider 2D Image | Azadironic acid | C28H38O5 |
| ***A. cepa*** |  |  |  |
|  | Cycloallin | [12305353](https://pubchem.ncbi.nlm.nih.gov/compound/12305353) | InChI=1/C6H11NO3S/c1-4-2-11(10)3-5(7-4)6(8)9/h4-5,7H,2-3H2,1H3,(H,8,9) |
|  | Gamma-s-propyl-cysteine | 13598411 | ChemSpider 2D Image | gamma-Glutamyl-S-propylcysteine | C11H20N2O5S |
|  | Isohamnetin 3,4-diglucoside | [5901757](https://pubchem.ncbi.nlm.nih.gov/compound/5901757) | InChI=1/C28H32O17/c1-40-13-4-9(2-3-12(13)42-27-23(38)21(36)18(33)15(7-29)43-27)25-26(20(35)17-11(32)5-10(31)6-14(17)41-25)45-28-24(39)22(37)19(34)16(8-30)44-28/h2-6,15-16,18-19,21-24,27-34,36-39H,7-8H2,1H3/t15-,16-,18-,19-,21+,22+,23-,24-,27-,28+/m1/s1 |
|  | Isorhamnetin 4-glucoside | [44259381](https://pubchem.ncbi.nlm.nih.gov/compound/44259381) | InChI=1/C16H12O7/c1-22-11-4-7(2-3-9(11)18)16-15(21)14(20)13-10(19)5-8(17)6-12(13)23-16/h2-6,17-19,21H,1H3 |
|  | Isorhamnetin | [5281654](https://pubchem.ncbi.nlm.nih.gov/compound/5281654) | ChemSpider 2D Image | Isorhamnetin | C16H12O7 |
|  | Isovallinin | [12127](https://pubchem.ncbi.nlm.nih.gov/compound/12127) | Isovanillin - Wikipedia |
|  | Kaempferol-3-O-rutinoside | [5318767](https://pubchem.ncbi.nlm.nih.gov/compound/5318767) | InChI=1/C27H30O15/c1-9-17(31)20(34)22(36)26(39-9)38-8-15-18(32)21(35)23(37)27(41-15)42-25-19(33)16-13(30)6-12(29)7-14(16)40-24(25)10-2-4-11(28)5-3-10/h2-7,9,15,17-18,20-23,26-32,34-37H,8H2,1H3/t9-,15+,17-,18+,20+,21-,22+,23+,26+,27-/m0/s1 |
|  | Luteolin | [5280445](https://pubchem.ncbi.nlm.nih.gov/compound/5280445) | ChemSpider 2D Image | Luteolin | C15H10O6 |
|  | Apigenin | [5280443](https://pubchem.ncbi.nlm.nih.gov/compound/5280443) | InChI=1/C15H10O5/c16-9-3-1-8(2-4-9)13-7-12(19)15-11(18)5-10(17)6-14(15)20-13/h1-7,16-18H |
|  | Methiin | [9578071](https://pubchem.ncbi.nlm.nih.gov/compound/9578071) | InChI=1/C4H9NO3S/c1-9(8)2-3(5)4(6)7/h3H,2,5H2,1H3,(H,6,7) |
|  | Quercetin 3,4-diglucoside | [5320835](https://pubchem.ncbi.nlm.nih.gov/compound/5320835) | File:Quercetin 3 4 diglucoside1.svg |
|  | Quercetin 3,7,4-triglucoside | 44259184 | InChI=1/C15H10O7/c16-7-4-10(19)12-11(5-7)22-15(14(21)13(12)20)6-1-2-8(17)9(18)3-6/h1-5,16-19,21H |
|  | Quercetin 3-glucoside | [5280804](https://pubchem.ncbi.nlm.nih.gov/compound/5280804) | 2D chemical structure of 18016-58-5 |
|  | Quercetin 7,4-diglucoside | [11968881](https://pubchem.ncbi.nlm.nih.gov/compound/11968881) | InChI=1/C15H10O7.H2O/c16-7-4-10(19)12-11(5-7)22-15(14(21)13(12)20)6-1-2-8(17)9(18)3-6;/h1-5,16-19,21H;1H2 |
|  | Quercetin | [5280343](https://pubchem.ncbi.nlm.nih.gov/compound/5280343) | InChI=1/C15H10O7/c16-7-4-10(19)12-11(5-7)22-15(14(21)13(12)20)6-1-2-8(17)9(18)3-6/h1-5,16-19,21H |
|  |  |  |  |
|  | Rutin | [5280805](https://pubchem.ncbi.nlm.nih.gov/compound/5280805) | InChI=1/C27H30O16/c1-8-17(32)20(35)22(37)26(40-8)39-7-15-18(33)21(36)23(38)27(42-15)43-25-19(34)16-13(31)5-10(28)6-14(16)41-24(25)9-2-3-11(29)12(30)4-9/h2-6,8,15,17-18,20-23,26-33,35-38H,7H2,1H3/t8-,15+,17-,18+,20+,21-,22+,23+,26+,27-/m0/s1 |
|  | s-propylcysteine | [125198](https://pubchem.ncbi.nlm.nih.gov/compound/125198) | ChemSpider 2D Image | S-Propylcysteine | C6H13NO2S |
|  | Zwiebelane | 29322215 | Zwiebelane |
|  | Apigenin | [5280443](https://pubchem.ncbi.nlm.nih.gov/compound/5280443) | InChI=1/C15H10O5/c16-9-3-1-8(2-4-9)13-7-12(19)15-11(18)5-10(17)6-14(15)20-13/h1-7,16-18H |
| ***X. aethiopica*** |  |  |  |
|  | Bornyl acetate | [6448](https://pubchem.ncbi.nlm.nih.gov/compound/6448) | ChemSpider 2D Image | l-Bornyl acetate | C12H20O2 |
|  | Carvone | [7439](https://pubchem.ncbi.nlm.nih.gov/compound/7439) | ChemSpider 2D Image | DL-carvone | C10H14O |
|  | Citral | [638011](https://pubchem.ncbi.nlm.nih.gov/compound/638011) | InChI=1/C10H16O/c1-9(2)5-4-6-10(3)7-8-11/h5,7-8H,4,6H2,1-3H3/b10-7+ |
|  | Citronellol | [8842](https://pubchem.ncbi.nlm.nih.gov/compound/8842) | InChI=1/C10H20O/c1-9(2)5-4-6-10(3)7-8-11/h5,10-11H,4,6-8H2,1-3H3/t10-/m1/s1 |
|  | Copaene | [12303902](https://pubchem.ncbi.nlm.nih.gov/compound/12303902) | ChemSpider 2D Image | Copaene | C15H24 |
|  | Cryptone | [92780](https://pubchem.ncbi.nlm.nih.gov/compound/92780) | ChemSpider 2D Image | cryptone | C9H14O |
|  | Cubebene | [91747196](https://pubchem.ncbi.nlm.nih.gov/compound/91747196) | InChI=1/C15H24/c1-9(2)12-6-5-11(4)15-8-7-10(3)13(15)14(12)15/h9,11-14H,3,5-8H2,1-2,4H3/t11-,12+,13-,14-,15+/m1/s1 |
|  | Cuminal | [326](https://pubchem.ncbi.nlm.nih.gov/compound/326) | ChemSpider 2D Image | Cuminaldehyde | C10H12O |
|  | Methy chavicol | 8815 | ChemSpider 2D Image | Estragole | C10H12O |
|  | Myrtenal | [61130](https://pubchem.ncbi.nlm.nih.gov/compound/61130) | ChemSpider 2D Image | (±)-Myrtenal | C10H14O |
|  | Terpiene-4-ol | 11230 | Terpinen-4-ol C10H18O, MONOTERPENE MONOTERPENE - Extrasynthese |
|  | Thymol | [6989](https://pubchem.ncbi.nlm.nih.gov/compound/6989) | ChemSpider 2D Image | Thymol | C10H14O |
|  | Trans carveol | [94221](https://pubchem.ncbi.nlm.nih.gov/compound/94221) | InChI=1/C10H16O/c1-7(2)9-5-4-8(3)10(11)6-9/h4,9-11H,1,5-6H2,2-3H3 |
|  | Verbenone | [29025](https://pubchem.ncbi.nlm.nih.gov/compound/29025) | InChI=1/C10H14O/c1-6-4-9(11)8-5-7(6)10(8,2)3/h4,7-8H,5H2,1-3H3/t7-,8+/m0/s1 |
|  | Alpha terpineol | [17100](https://pubchem.ncbi.nlm.nih.gov/compound/17100) | ChemSpider 2D Image | Terpineol | C10H18O |